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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/014,220	11/09/2001	Che-Kun James Shen	514162000120	5165

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EXAMINER
KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
1636	5

DATE MAILED: 06/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/014,220	SHEN, CHE-KUN JAMES	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *29 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-20 are pending and are examined in this office action.

► *Applicants are advised to follow Amendment Practice under revised 37 CFR §1.121 (http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm). Each amendment document that includes a change to an existing claim, or submission of a new claim, **must include a complete listing of all claims** in the application. After each claim number, the status must be indicated in a parenthetical expression, and the text of each claim under examination (with markings to show current changes) must be presented. The listing will serve to replace all prior versions of the claims in the application.*

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-10 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2 of copending Application No. 09/961,563. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of non-human transgenic animals as

claimed in the pending U.S. App. No. 09/961,563 encompasses the non-mouse/non-human animals as claimed in the instant application. For example the scope of non-human transgenic animals as claimed in the pending U.S. App. No. 09/961,563 encompasses a transgenic rat, cow, rabbit, goat, guinea pig, baboon, squirrel, monkey, chimpanzee, frog, toad chicken, turkey and sheep as claimed in the instant application. In addition the transgene construct as claimed in the 09/961563, which comprises "(1) a transcriptional start site; (2) a promoter operably linked to the transcriptional start site; and (3) an enhancer operably linked to the promoter, the enhancer comprising the nucleotide sequence of SEQ ID NO:1, wherein the transgenic animal expresses a transcript driven by the promoter, the level of expression in at least one cell type of the animal being proportionally dependent on the copy number of the transgene" is identical to the transgene construct as claimed in the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for enabling for a transgenic pig (HS40(mt)-ζ597hGH), whose somatic and germ line cells contain a transgene comprising a transcriptional start site, the human ζ-globin

promoter operably linked to a transcriptional start site and a mutant human HS-40 enhancer (SEQ ID NO:1) operably linked to the ζ-globin promoter which drives the expression of human growth hormone in erythroblasts, does not reasonably provide enablement for any and all transgenic non-mouse non-human animals wherein the transgene encodes a transcriptional start site and an enhancer operably linked to any and all kind of promoter that leads to expression of transgene transcripts in all type of cells in the transgenic animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature Of Invention:

Invention relates to transgenic animals.

Breadth Of Claims And Guidance Provided By The Inventor:

The scope of instant claim encompasses any and all non-mouse non-human transgenic animals (insects, fish reptiles, birds, whales, horses and various primates), whose somatic and germ line calls contain a transgene (as claimed). The scope of transgene encompasses the presence of any and all promoters operatively linked to nucleotide sequences encoding any and all polypeptides of interest. In addition the scope of invention as claimed encompasses the expression of transgene transcripts in at least one type of cells. The specification as filed teaches a DNA-construct that encodes a transgene comprising a transcriptional start site, the human ζ-globin promoter operably linked to a transcriptional start site and a mutant human HS-40 enhancer operably linked to the ζ-globin promoter, which drives the expression of human growth hormone. In addition, the specification discloses a transgenic pig (HS40(mt)-ζ597hGH) that express human growth hormone in the blood (spec page 19; page pages 24-26, table-2, table-3,

table-4). Besides a transgenic pig (HS40(mt)-ζ597hGH) that expresses hGH in the blood, the instant specification fails to disclose any other non-mouse non-human transgenic animal (rat, cow, rabbit, goat, guinea pig, baboon, squirrel, monkey, chimpanzee, frog, toad chicken turkey and sheep) encoding the transgene (as claimed), wherein the transgene encodes any and all polypeptides of interest.

State Of Art And Predictability:

The *state of transgenic art* at the time of filing was such that phenotype of an animal is determined by a complex interaction of genetics and environment. (Wood. Comp. Med. 50(1): 12-15, 2000, see page12). The phenotype examined in a transgenic and knock out model is influenced by genetic background, which is the collection of all genes present in an organism that influence a trait or traits. The genes may be part of same biochemical or signaling pathway or of an opposing pathway or may appear unrelated to the gene being studied. Furthermore, allelic variations and the interactions between the allelic variants also influence a particular phenotype. These epigenetic effects can dramatically alter the observed phenotype and therefore can influence or later the conclusions drawn form the transgenic or knockout models (Sigmund, Arterioscler. Throm. Vasc. Biol.20:1425-1429, 2000, see page 1425).

The transgene expression and physiological consequences of transgene products in non-mouse mammals are not always accurately predicted among various species of mammals (Wall RJ Theriogenology 45:57-68, 1996). Transgene efficiency is low, and range from 1% in farm animals (cattle, sheep, pigs) to 3% in laboratory animals like rabbits, mice and rats (Wall, see page 61). Furthermore, the lack of understanding of essential genetic control elements make it difficult to predict the behavior of a transgene in any and all animals because the expression is

influenced by position effect in transgenic animals. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct and the site of integration, are the important factors that govern the expression of a transgene (Wall, page 61-62). The cis-acting elements of one species may interact with different transactivating factors in other species. For example, the introduction of human growth hormone transgene in mice results in mammoth mouse phenotype, where as expression of the same transgene in pig results in premature death of transgenic pigs. (Pursel VG et al J. Reprod Fert. Sup 40: 235-245 1990, see page 235, para.1). Furthermore, many biochemical pathways are plastic in nature, which reflects the ability of the embryo to use alternative gene when the preferred gene is modified. It is known in the art that the level and the specificity of a transgene as well as the phenotype of the transgenic animal are greatly dependent upon the specific expression vector used. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct and the site of integration, for example are the important factors that govern the expression of a transgene. (Kappel et al. Current Opinion in Biotechnology 3:558-553 1992; see page 550, col.1, para. 3-4, page 548, col.2 para.2). In instant case considering the limited disclosure wherein a transgenic pig has been made by using (HS40(mt)-ζ597hGH) transgene construct, it is highly unpredictable that the transgene construct other than HS40(mt)-ζ597hGH would certainly lead to development of mature transgenic pigs that express hGH. In addition it is highly unpredictable that a transgene construct comprising a mammalian ζ-globin promoter operably linked to a mammalian erythroid specific enhancer region would results in the tissue specific expression of the transgene product in non-mammalian animals like frog, toad, chicken and turkey.

Quantity Of Experimentation Required:

Thus, in view of lack of specific guidance in the specification and considering the unpredictability in the transgenic art, the skilled artesian at the time of filing would be unable to use the invention as claimed, without an excessive and undue amount of experimentation. The quantity of experimentation required would include the functional and structural characterization of any and all transgene constructs comprising all possible combinations of any promoter(s), enhancer element(s) and any gene(s) of interest. The quantity of experimentation required would further include making of any and all kind of transgenic animals like all types of insects, fish, birds, reptiles and mammals encoding any and all types of transgene constructs. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). In instant case making various species of transgenic animals across the "Animal Kingdom" is not considered routine in the art and without sufficient guidance to a method of making a particular species the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

3. Claims 11-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature Of Invention:

Invention relates to a method of gene therapy.

Breadth Of Claims And Guidance Provided By The Inventor:

The scope of invention as claimed encompasses a method of expressing a transcript in an animal by administering to the animal an expression vector (viral or non-viral) via any and all route of administration (local, systemic, oral, nasal etc) using any and all means (injection, feeding, surface application etc). At best the instant specification suggests that the nucleic acid can be administered by parental injection or via viral expression vector (spec. page 6, lines 1-4). The instant specification fails to provide any guidance regarding how to deliver a vector via any l route of administration in vivo so that one skill in the art would be able to express the transgene in a target cell of interest in-vivo. For example, the specification fails to disclose how one skill in the art would delivery the transgene to a particular blood cell type (e.g. a hematopoietic stem cell) via systemically administering a vector containing the claimed genetic construct. At best the specification only teaches the making a transgenic mouse by microinjection of a DNA fragment into the pronucleus of an embryo (Spec. Page 21, lines 2-3), which does not contemplate the delivery of a transgene via a method of gene therapy. The successful expression of a transgene construct into a target cell in-vivo not only depends upon the type of vector selected but also to the susceptibility of host cells to that vector. The specification fails to show that the administration of any viral or non viral vector comprising the clamed genetic construct results in the expression of transcript of interest in vivo.

State Of Art And Predictability:

The gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy. (Rosenberg et al, Science 287:1751, 2000, Verma, Mol. Ther. 1: 493, 2000, Friedmann, Science 287(5461):2163-5, 2000, Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997, Touchette, Nat. Med. 2(1) 7-8, 1996). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectations of current gene therapy protocols have been over sold without any apparent success (Touchette page 7, col.1 para. 2; page 8, col.2 para 1-4). The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease. (Touchette, page 7, col.3, para.3). In instant case the scope of invention as claimed encompasses the expression of a transcript of interest in an animal via method of gene delivery. Even though the method as claimed only requires the expression of a transcript of interest, the specification fails to disclose how to use a particular transcript of interest especially in context with a specific disease, disorder or abnormality.

Furthermore, it has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors (Verma et al, see page 239 col.3 par.2, page 242, table-2).

Although the retroviral vectors are the vectors of choice, they require target cells to be in cycling state for the successful delivery of gene of interest. On the other hand vector comprising DNA viruses and liposome coated DNA have been used to transduce non-dividing cells but this results in a transient expression due to non-integration of transgenes in host cells (Verma et al page 242, table-2). In addition, the use of adenoviral and adeno associated viral vector is also problematic because these vectors elicits considerable immune response in vivo, which affects the sustained expression of the transduced genes (Verma et al, page 241, col.1, par.3; col.3, par.1). Furthermore, in vitro gene transfer studies are not predictive of in vivo gene therapy because gene transfer frequency is much higher in-vitro models where most of cells are under going rapid cell division, which is quite not the case in vivo environment. Besides the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacles to overcome. The viral particles binds to many cells they encounter in vivo and therefor would be diluted out before reaching their targets (Anderson WF, page 25 col.2, para.4). In instant case given the broadest reasonable interpretation the scope of invention as claimed encompasses administering of any viral or non-viral vector via any and route of administration via any and all means. Even though, the gene therapy holds much promise to come, the success will only be achieved through continued rigorous research on the most fundamental mechanisms that contribute to a genetic disease along with the pathogenesis of the disease, gene delivery and gene expression in animals

Quantity Of Experimentation Required:

In instant case gene based delivery of gene products (in-vivo) is not considered routine in the art and without sufficient guidance to a specific method of administration and a therapeutic

gene of interest the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed. The undue experimentation required would include making any and all viral or non-viral vectors encoding a transcript of interest (as claimed), the administration of the vector via any and all route of administration to target any and all cell types in-vivo, followed by an evaluation of the expression of gene product.

Claim Objections

4. Claims 2 and 12 are objected to because of the following informalities: The instant claims recites claim limitation "bird, frog, toad, chicken, turkey" in line 3. Since the instant claims seem to recite individual animal species (chicken, turkey) deletion of word "bird" (group comprising chicken and turkey) has been suggested. Appropriate correction is required.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-

6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-8724 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
Patent examiner

SUMESH KAUSHAL
PATENT EXAMINER